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THE MERCK MANUAL OF DIAGNOSIS AND THERAPY

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FOREWORD

With this edition, *The Merck Manual* celebrates its 100th birthday. When the editors of the 1st Edition produced their 192-page compendium, they could not have realized the extent to which medical knowledge would explode over the next century. *The Merck Manual* now fills 2,655 pages and covers countless diseases that were not known 100 years ago. A brief review of medical practice as reflected in *The Merck Manual* during the past century follows on page vii.

Although the knowledge of medicine has grown, the goal of *The Merck Manual* has not changed—To provide useful clinical information to practicing physicians, medical students, interns, residents, nurses, pharmacists, and other health care professionals in a concise, complete, and accurate manner. *The Merck Manual* continues to cover all the subjects expected in a textbook of internal medicine as well as detailed information on pediatrics, psychiatry, obstetrics, gynecology, dermatology, pharmacology, ophthalmology, otolaryngology, and a number of special subjects. *The Merck Manual* quickly provides information that helps practitioners achieve optimal care. The more specialized the practice of medicine becomes, the more important such information becomes. Specialists as well as generalists must at some time quickly access information about other specialties.

The 17th edition of *The Merck Manual* is the culmination of an arduous but rewarding 7-year enterprise. Every topic has been updated, and many have been completely rewritten. Topics new to this edition include hand disorders, prion diseases, death and dying, probabilities in clinical medicine, multiple chemical sensitivity, chronic fatigue syndrome, rehabilitation, smoking cessation, and drug therapy in the elderly, among others. The members of the Editorial Board, special consultants, and contributing authors are listed on the following pages with their affiliations. They deserve a degree of gratitude that cannot be adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

Because of the extensive subject matter covered and a successful tradition developed through trials of successes and failures, *The Merck Manual* has some unique characteristics. We urge readers to spend a few minutes reviewing the Guide for Readers (p. xii), the Table of Contents at the beginning of each section (indicated by a thumb tab), and the Index (p. 2657). Subject headings within each section, internal headings within a subject discussion, and boldfaced terms in the text form an outline intended to help with use of the text.

We hope this edition of *The Merck Manual* will serve as an aid to you, our readers, compatible with your needs and worthy of frequent use. Suggestions for improvements will be warmly welcomed and carefully considered.

MARK H. BEERS, M.D., and ROBERT BERKOW, M.D., *Editors*

SECTION 22

CLINICAL PHARMACOLOGY

298 / DRUG INPUT AND DISPOSITION

Drugs are almost always compounds foreign to the body. As such, they, unlike endogenous substances, are not continually being formed and eliminated. Drug absorption, bioavailability, distribution, and elimination are therefore determinants of onset, duration, and intensity of drug effect.

ABSORPTION

Process of drug movement from the administration site to the systemic circulation.

Drug absorption is determined by physicochemical properties of drugs, their formulations, and routes of administration. **Drug products**—the actual dosage forms (eg, tablets, capsules, solutions), consisting of the drug plus other ingredients—are formulated to be administered by various routes, including oral, buccal, sublingual, rectal, parenteral, topical, and inhalational. A prerequisite to absorption is drug dissolution. Solid drug products (eg, tablets) disintegrate and deaggregate, but absorption can occur only after drugs enter solution.

Transport Across Cell Membranes

When given by most routes (excluding IV), a drug must traverse several semipermeable cell membranes before reaching the systemic circulation. These membranes are biologic barriers that selectively inhibit the passage of drug molecules and are composed primarily of a bimolecular lipid matrix, containing mostly cholesterol and phospholipids. The lipids provide stability to the membrane and determine its permeability characteristics. Globular proteins of various sizes and composition are embedded in the matrix; they are involved in transport and function as receptors for cellular regulation. Drugs may cross a biologic barrier by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis.

Passive diffusion: In this process, transport across a cell membrane depends on the concentration gradient of the solute. Most drug molecules are transported across a membrane by simple diffusion from a region of high concentration (eg, GI fluids) to one of low concentration (eg, blood). Because drug molecules are rapidly removed by the systemic circulation and distributed into a large volume of body fluids and tissues, drug concentration in blood is initially low compared with that at the administration site, producing a large gradient. The diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, degree of ionization, and size and on the area of the absorptive surface. Because the cell membrane is lipoid, lipid-soluble drugs diffuse more rapidly than relatively lipid-insoluble drugs. Small molecules tend to penetrate membranes more rapidly than large ones.

Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble and diffuses readily across cell membranes. The ionized form cannot penetrate the cell membrane easily because of its low lipid solubility and high electrical resistance, resulting from its charge and the charged groups on the cell membrane surface. Thus, drug penetration may be attributed mostly to the un-ionized form. Distribution of an ionizable drug across a membrane at equilibrium is determined by the drug's pK_a (the pH at which concentrations of un-ionized and ionized forms of the drug are equal) and the pH gradient, when present. For a weak acid, the higher the pH, the lower the ratio of un-ionized to ionized forms. In plasma (pH, 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a pK_a of 4.4) is 1:1000; in gastric fluid (pH, 1.4), the ratio is reversed (1000:1). When the weak acid is given orally, the concentration gradient for un-ionized drug between stomach and plasma tends to be large, favoring diffusion through the gastric mucosa. At equilibrium, the concentrations of un-ionized drug in the stomach and in the plasma are equal because only un-ionized drug can penetrate the membranes; the concentration of ionized drug in the plasma would then be about 1000 times greater than that in the stomach. For a weak base with a pK_a of 4.4, the outcome is reversed. Thus theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weak bases (eg, quinidine). However, whether a drug is acidic or basic, most of its absorption occurs in the small intestine (see Oral Administration, below).

Facilitated passive diffusion: For certain molecules (eg, glucose), the rate of membrane penetration is greater than expected from their low lipid solubility. One theory is that a carrier component combines reversibly with the substrate molecule at the cell membrane exterior, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. Carrier-mediated diffusion is characterized by selectivity and saturability: The carrier transports only substrates with a relatively specific molecular configuration, and the process is limited by the availability of carriers. The process does not require energy expenditure, and transport against a concentration gradient does not occur.

Active transport: This process is characterized by selectivity and saturability and requires energy expenditure by the cell. Substrates may accumulate intracellularly against a concentration gradient. Active transport appears to be limited to drugs structurally similar to endogenous substances. These drugs are usually absorbed from sites in the small intestine. Active transport processes have been identified for various ions, vitamins, sugars, and amino acids.

Pinocytosis: Fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. This mechanism also requires energy expenditure. Pinocytosis probably plays a minor role in drug transport, except for protein drugs.

Oral Administration

For oral administration, the most common route, absorption refers to the transport of drugs across membranes of the epithelial cells in the GI tract. Absorption after oral administration is confounded by differences in luminal pH along the GI tract, surface area per luminal volume, blood perfusion, the presence of bile and mucus, and the nature of epithelial membranes. Acids are absorbed faster in the intestine than in the stomach, apparently contradicting the hypothesis that un-ionized drug more readily crosses membranes. However, the apparent contradiction is explained by the larger surface area and greater permeability of the membranes in the small intestine.

The oral mucosa has a thin epithelium and a rich vascularity that favors absorption, but contact is usually too brief, even for drugs in solution, for appreciable absorption to occur. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer so that absorption is more complete.

The stomach has a relatively large epithelial surface, but because it has a thick mucous layer and the time that the drug remains there is usually relatively short, absorption is limited. Absorption of virtually all drugs is faster from the small intestine than from the stomach. Therefore, gastric emptying is the rate-limiting step. Food, especially fatty foods, slows gastric emptying (and the rate of drug absorption), explaining why some drugs should be taken on an empty stomach when a rapid onset of action is desired. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect. Drugs that affect gastric emptying (eg, parasympatholytic drugs) affect the absorption rate of other drugs.

The small intestine has the largest surface area for drug absorption in the GI tract. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. GI microflora may inactivate certain drugs, reducing their absorption. Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and decrease absorption by passive diffusion. (Decreased peripheral blood flow also alters drug distribution and metabolism.)

Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are too polar (ie, poorly lipid-soluble) to cross membranes readily (eg, many antibiotics). For such drugs, transit may be too rapid for absorption to be complete.

For controlled-release dosage forms, absorption may occur primarily in the large intestine, particularly when drug release continues for > 6 h, the time for transit to the large intestine.

Absorption from solution: A drug given orally in solution is subjected to numerous GI secretions and, to be absorbed, must sur-

vive encounters with low pH and potentially degrading enzymes. Usually, even if a drug is stable in the enteral environment, little of it remains to pass into the large intestine. Drugs with low lipophilicity (ie, low membrane permeability), such as aminoglycosides, are absorbed slowly from solution in the stomach and small intestine; for such drugs, absorption in the large intestine is expected to be even slower because the surface area is smaller. Consequently, these drugs are not candidates for controlled release.

Absorption from solid forms: Most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. These products must disintegrate and dissolve before absorption can occur. Disintegration greatly increases the drug's surface area in contact with GI fluids, thereby promoting drug dissolution and absorption. Disintegrants and other excipients (eg, diluents, lubricants, surfactants, binders, dispersants) are often added during manufacture to facilitate these processes. Surfactants increase the dissolution rate by increasing the wetability, solubility, and dispersibility of the drug. Disintegration of solid forms may be retarded by excessive pressure applied during the tableting procedure or by special coatings applied to protect the tablet from the digestive processes of the gut. Hydrophobic lubricants (eg, magnesium stearate) may bind to the active drug and reduce its bioavailability.

Dissolution rate determines the availability of the drug for absorption. When slower than absorption, dissolution becomes the rate-limiting step. Overall absorption can be controlled by manipulating the formulation. For example, reducing the particle size increases the drug's surface area, thus increasing the rate and extent of GI absorption of a drug whose absorption is normally limited by slow dissolution. Dissolution rate is affected by whether the drug is in salt, crystal, or hydrate form. The Na salts of weak acids (eg, barbiturates, salicylates) dissolve faster than their corresponding free acids regardless of the pH of the medium. Certain drugs are polymorphic, existing in amorphous or various crystalline forms. Chloramphenicol palmitate has two forms, but only one sufficiently dissolves and is absorbed to be clinically useful. A hydrate is formed when one or more water molecules combine with a drug molecule in crystal form. The solubility of such a solvate may markedly differ from the nonsolvated form; eg, anhydrous ampicillin has a greater rate of dissolution and absorption than its corresponding trihydrate.

Parenteral Administration

Direct placement of a drug into the bloodstream (usually IV) ensures delivery of the dose to the systemic circulation. However, delivery of the entire dose is not ensured if a route requires movement through one or more biologic membranes to reach the systemic circulation (IM or sc injection). For protein drugs with a molecular mass > 20,000 g/mol, movement across capillary membranes is so slow that after IM or sc administration, most absorption occurs via the lymphatic system by default. In such cases, the delivery rate to systemic circulation is slow and often incomplete because of first-pass metabolism by proteolytic enzymes in the lymphatics.

Because capillaries tend to be highly porous, perfusion (blood flow/gram of tissue) greatly affects the absorption rate of small molecules. Thus, the injection site can markedly influence a drug's absorption rate; eg, the absorption rate of diazepam injected IM into a site with poor blood flow can be much slower than that after oral administration.

Absorption may be delayed or erratic when salts of poorly soluble acids and bases are injected IM. The parenteral form of phenytoin is a 40% propylene glycol solution of the Na salt with a pH of about 12. When the solution is injected IM, the propylene glycol is absorbed, and the tissue fluids, acting as a buffer, decrease the pH, shifting the equilibrium between the ionized and free acid forms of the drug. The poorly soluble free acid then precipitates. As a result, dissolution and absorption take 1 to 2 wk to occur.

Controlled-Release Forms

Controlled-release dosage forms are designed to reduce dosing frequency and to reduce fluctuation in plasma drug concentration, providing a more uniform therapeutic effect. Less frequent dosing is more convenient and may improve patient compliance. These dosage forms are suitable for drugs that otherwise require frequent dosing because elimination half-life and duration of effect are short.

Oral controlled-release forms are often designed to maintain therapeutic drug concentrations for ≥ 12 h. The absorption rate can be controlled by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix from which it is released slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins.

Transdermal controlled-release forms are designed to provide drug release for extended periods; eg, clonidine diffusion through a membrane provides controlled drug delivery for 1 wk, and nitroglycerin-impregnated polymer bonded to an adhesive bandage provides controlled drug delivery for 24 h. Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.

Many nonintravenous parenteral preparations are formulated to sustain blood levels. For antimicrobials, relatively insoluble salts (eg, penicillin G benzathine) injected IM provide therapeutic concentrations for extended periods. For others, suspensions or solutions in nonaqueous vehicles (eg, insulin injected in crystalline suspensions) are formulated. Amorphous insulin, with a high surface area for dissolution, has a rapid onset and short duration of action.

BIOAVAILABILITY

Extent to which—and sometimes rate at which—the active moiety (drug or metabolite) enters systemic circulation, thereby gaining access to the site of action.

The physicochemical properties of a drug govern its absorptive potential, but the properties of the dosage form (which partly depend on its design and manufacture) can largely determine drug bioavailability. Differences in bioavailability among formulations of a given drug can have clinical significance. Thus, the concept of equivalence among drug products is important in making clinical decisions. **Chemical equivalence** refers to drug products that contain the same compound in the same amount and that meet current official standards; however, inactive ingredients in drug products may differ. **Bioequivalence** refers to chemical equivalents that, when administered to the same person in the same dosage regimen, result in equivalent concentrations of drug in blood and tissues. **Therapeutic equivalence** refers to drug products that, when administered to the same person in the same dosage regimen, provide essentially the same therapeutic effect or toxicity. Bioequivalent products are expected to be therapeutically equivalent.

Therapeutic problems (eg, toxicity, lack of efficacy) are encountered most frequently during long-term therapy when a patient who is stabilized on one formulation is given a nonequivalent substitute (as for digoxin or phenytoin).

Sometimes therapeutic equivalence may be achieved despite differences in bioavailability. For example, the therapeutic index (ratio of the maximum tolerated dose to the minimum effective dose) of penicillin is so wide that moderate blood concentration differences due to bioavailability differences in penicillin products may not affect therapeutic efficacy or safety. In contrast, bioavailability differences are important for a drug with a relatively narrow therapeutic index.

The physiologic characteristics and comorbidities of the patient also affect bioavailability.

Absorption rate is important because even when a drug is absorbed completely, it may be absorbed too slowly to produce a therapeutic blood level quickly enough or so rapidly that toxicity results from high drug concentrations after each dose.

Causes of Low Bioavailability

When a drug rapidly dissolves and readily crosses membranes, absorption tends to be complete, but absorption of orally administered drugs is not always complete. Before reaching the vena cava, a drug must move down the GI tract and pass through the gut wall and liver, common sites of drug metabolism (see Ch. 43); thus, a drug may be metabolized (first-pass metabolism) before it can be measured in the systemic circulation. Many drugs have low oral bioavailability because of extensive first-pass metabolism. For such drugs (eg, isoproterenol, norepinephrine, testosterone), extraction in these tissues is so extensive that bioavailability is virtually zero. For drugs with an active metabolite, the therapeutic consequence of first-pass metabolism depends on the contri-

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butions of the drug and the metabolite to the desired and undesired effects.

Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. More factors can affect bioavailability when absorption is slow or incomplete than when it is rapid and complete, so slow or incomplete absorption often leads to variable therapeutic responses.

Insufficient time in the GI tract is a common cause of low bioavailability. Ingested drug is exposed to the entire GI tract for no more than 1 to 2 days and to the small intestine for only 2 to 4 h. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low. Age, sex, activity, genetic phenotype, stress, disease (eg, achlorhydria, malabsorption syndromes), or previous GI surgery can affect drug bioavailability.

Reactions that compete with absorption can reduce bioavailability. They include complex formation (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the gut wall (eg, sulfoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin and cholestyramine), and metabolism by luminal microflora.

Assessment of Bioavailability

Assessment of bioavailability from plasma concentration-time data usually involves determining the maximum (peak) plasma drug concentration, the time at which maximum plasma drug concentration occurs (peak time), and the area under the plasma concentration-time curve (AUC—see FIG. 298-1). The plasma drug concentration increases with the extent of absorption; the peak is reached when the drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma concentration can be misleading, because drug elimination begins as soon as the drug enters the bloodstream. The most widely used general index of absorption rate is peak time; the slower the absorption, the later the peak time. However, peak time is often not a good statistical measure because it is a discrete value that depends on frequency of blood sampling and, in the case of relatively flat

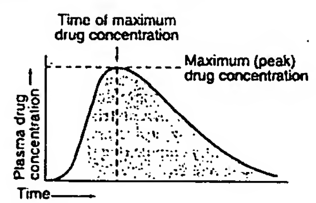

FIG. 298-1. Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug. Area under the plasma concentration-time curve is indicated by shading.

concentrations near the peak, on assay reproducibility.

AUC is the most reliable measure of bioavailability. It is directly proportional to the total amount of unchanged drug that reaches the systemic circulation. For an accurate measurement, blood must be sampled frequently over a long enough time to observe virtually complete drug elimination. Drug products may be considered bioequivalent in extent and rate of absorption if their plasma-level curves are essentially superimposable. Drug products that have similar AUCs but differently shaped plasma-level curves are equivalent in extent but differ in their absorption rate-time profiles.

Single vs. multiple doses: Bioavailability may be assessed after single or repetitive (multiple) dosing. More information about rate of absorption is available after a single dose than after multiple dosing. However, multiple dosing more closely represents the usual clinical situation, and plasma concentrations are usually higher than those after a single dose, facilitating data analysis. After multiple dosing at a fixed-dosing interval for four or five elimination half-lives, the blood drug concentration should be at steady state (the amount absorbed equals the amount eliminated within each dosing interval). The extent of absorption can then be analyzed by measuring the AUC during a dosing interval. Measuring the AUC over 24 h is probably preferable because of circadian variations in physiologic functions and because of possible variations in dosing intervals and absorption rates during a day.

For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7 to 10 elimination half-lives for complete urinary recovery of the absorbed drug. Bioavailability may also be assessed after multiple dosing by measuring unchanged drug recovered from urine over 24 h under steady-state conditions.

DISTRIBUTION

After a drug enters the systemic circulation, it is distributed to the body's tissues. Distribution is generally uneven because of differences in blood perfusion, tissue binding, regional pH, and permeability of cell membranes.

The entry rate of a drug into a tissue depends on the rate of blood flow to the tissue, on tissue mass, and on partition characteristics between blood and tissue. Distribution equilibrium (when entry and exit rates are the same) between blood and tissue is reached more rapidly in richly vascularized areas than in poorly perfused areas, unless diffusion across membrane barriers is the rate-limiting step. After equilibrium is attained, drug concentrations (bound and unbound—see below) in tissues and in extracellular fluids are reflected by the plasma concentration. Metabolism and excretion occur simultaneously with distribution, making the process dynamic and complex (see also Ch. 299).

Apparent Volume of Distribution

The volume of fluid into which a drug appears to be distributed or diluted is called the apparent volume of distribution (the fluid volume required to contain the drug in the body at the same concentration as in plasma). This parameter provides a reference for the plasma concentration expected for a given dose and for the dose required to produce a given concentration. However, it provides little information about the specific pattern of distribution. Each drug is uniquely distributed in the body. Some drugs go into fat, others remain in the ECF, and still others are bound avidly to specific tissues, commonly liver or kidney.

Many acidic drugs (eg, warfarin, salicylic acid) are highly protein-bound and thus have a small apparent volume of distribution. Many basic drugs (eg, amphetamine, meperidine) are avidly taken up by tissues and thus have an apparent volume of distribution larger than the volume of the entire body.

Binding

The extent of drug distribution into tissues depends on the extent of plasma protein and tissue binding.

Plasma protein binding: Drugs are transported in the bloodstream partly in solution as free (unbound) drug and partly bound to blood components (eg, plasma proteins, blood cells). The ratio of bound to unbound drug in plasma is mainly determined by the reversible interaction between a drug and the plasma protein to which it binds, as governed by the law of mass action. Many plasma proteins can interact with drugs. Albumin, α_1-acid glycoprotein, and lipoproteins are most important. Acidic drugs are generally bound more extensively to albumin, and basic drugs to α_1-acid glycoprotein and/or lipoproteins (see TABLE 298-1).

Only unbound drug is thought to be available for passive diffusion to extravascular or tissue sites where pharmacologic effects occur. Therefore, the unbound drug concentration may be more closely related to drug concentration at the active site and to drug effects, often making the fraction unbound (ratio of unbound to total concentrations) a more useful parameter than the fraction bound. Plasma protein binding influences distribution and the apparent relationship between pharmacologic activity and total

TABLE 298-1. EXTENT OF BINDING IN PLASMA FOR SELECTED DRUGS

Drug	% Bound	% Unbound
Warfarin	99.5	0.5
Diazepam	99	1
Furosemide	96	4
Dicloxacillin	94	6
Propranolol*	93	7
Phenytoin	89	11
Quinidine*	71	29
Lidocaine*	51	49
Digoxin	25	75
Gentamicin	3	97
Atenolol	~0	~100

*Significant binding to α_1-acid glycoprotein and/or lipoproteins.

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plasma drug concentration. At high drug concentrations, the amount of bound drug approaches an upper limit depending on the number of available binding sites, resulting in **saturability.** Saturability is the basis of displacement interactions among drugs (see DRUG INTERACTIONS in Ch. 301).

Tissue binding: Drugs bind to many substances other than proteins. Binding may be very specific, as when chloroquine binds with nucleic acids. Binding usually occurs when a drug associates with a macromolecule in an aqueous environment but may occur when a drug is partitioned into body fat. Because fat is poorly perfused, equilibration time is long, especially if the drug has a high affinity for fat.

Drug reservoir: Accumulation of drugs in tissues or body compartments can prolong the sojourn of drug in plasma and drug action because the tissues release stored drug as the plasma concentration declines. Location of the active site and relative differences in tissue distribution can also be important. For the anesthetic thiopental, storage in tissue reservoirs initially shortens the drug effect but after repeated administration prolongs it. Thiopental is highly lipid soluble and rapidly distributes to the brain after a single IV injection. After a single dose, thiopental concentration in the brain increases for a few minutes, then declines parallel with the plasma concentration. Anesthesia ends rapidly as the drug redistributes to more slowly perfused tissues. However, if plasma concentration is monitored long enough, a third phase of distribution, in which the drug is slowly released from fat, can be distinguished. With continued administration of thiopental, large amounts may be stored in fat, resulting in prolongation of anesthetic plasma concentrations.

Some drugs accumulate, producing higher concentrations in cells than in ECF, most commonly because they bind with protein, phospholipids, or nucleic acids. Antimalarial drugs (eg, chloroquine) produce concentrations within WBCs and liver cells thousands of times higher than those in plasma. The stored drug is in equilibrium with drug in plasma and moves into plasma as the drug is eliminated from the body.

Blood-Brain Barrier

Drugs reach the CNS via brain capillaries and via CSF. Although the brain receives about 1/6 of cardiac output, distribution of drugs to brain tissue is restricted. Some lipid-soluble drugs (eg, thiopental) enter the brain and exert their pharmacologic effects rapidly, but many drugs, particularly the more water-soluble drugs, enter the brain slowly. The endothelial cells of the brain capillaries, which appear to be more tightly joined to one another than are those of other capillaries, contribute to the slow diffusion of water-soluble drugs. Another barrier to water-soluble drugs is the glial connective tissue cells (astrocytes), which form an astrocytic sheath close to the basement membrane of the capillary endothelium. The capillary endothelium and the astrocytic sheath form the blood-brain barrier. Because the capillary wall rather than the parenchymal cell forms the barrier, the brain's permeability characteristics differ from those of other tissues. Thus, polar compounds cannot enter the brain but can enter the interstitial fluids of most other tissues. The observation that polar dyes enter most tissues but not the CNS led to the concept of the blood-brain barrier.

Drugs may enter ventricular CSF directly via the choroid plexus, entering brain tissue by passive diffusion from CSF. Also in the choroid plexus, organic acids (eg, penicillin) are actively transported from CSF to blood.

The drug penetration rate into the CSF or into other tissue cells is determined mainly by the extent of protein binding, the degree of ionization, and the lipid-water partition coefficient of the drug. The penetration rate into the brain is slow for highly protein-bound drugs and can be so slow for the ionized form of weak acids and bases as to be virtually nonexistent.

Because the CNS is so well perfused, permeability is generally the major determinant of the drug distribution rate. However, for the interstitial fluids of most tissues, perfusion is a major determinant. For poorly perfused tissues (eg, muscle, fat), distribution is very slow, especially if the tissue has a high affinity for the drug.

ELIMINATION

Sum of the processes of drug loss (metabolism and excretion) from the body.

METABOLISM

The liver is the principal site of drug metabolism (chemical alteration) in the body.

TABLE 298–2. SELECTED DRUGS WITH THERAPEUTICALLY IMPORTANT METABOLITES

Drug	Metabolite
Acetohexamide	Hydroxyhexamide
Amitriptyline	Nortriptyline
Aspirin*	Salicylic acid
Chloral hydrate*	Trichloroethanol
Chlordiazepoxide	Desmethylchlordiazepoxide
Codeine	Morphine
Diazepam	Desmethyldiazepam
Flurazepam	Desethylflurazepam
Glutethimide	4-Hydroxyglutethimide
Imipramine	Desipramine
Lidocaine	Desethyllidocaine
Meperidine	Normeperidine
Phenacetin*	Acetaminophen
Phenylbutazone	Oxyphenbutazone
Prednisone*	Prednisolone
Primidone*	Phenobarbital
Procainamide	*N*-acetylprocainamide
Propranolol	4-Hydroxypropranolol

*Pro-drugs; metabolites are primarily responsible for their therapeutic effects.

Some metabolites are pharmacologically active (see TABLE 298–2). An inactive substance that has an active metabolite is called a pro-drug, especially if designed to deliver the active moiety more effectively.

Pathways of Metabolism

Drug metabolism involves a wide range of chemical reactions, including oxidation, reduction, hydrolysis, hydration, conjugation, condensation, and isomerization. The enzymes involved are present in many tissues but generally are more concentrated in the liver. For many drugs, metabolism occurs in two apparent phases. Phase I reactions involve the formation of a new or modified functional group or a cleavage (oxidation, reduction, hydrolysis); these are nonsynthetic reactions. Phase II reactions involve conjugation with an endogenous compound (eg, glucuronic acid, sulfate, glycine) and are therefore synthetic reactions. Metabolites formed in synthetic reactions are more polar and more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. Some drugs undergo either phase I or phase II reactions; thus, phase numbers reflect functional rather than sequential classification.

Cytochrome P-450: The most important enzyme system of phase I metabolism is cytochrome P-450, a microsomal superfamily of isoenzymes that transfer electrons and thereby catalyze the oxidation of many drugs. The electrons are supplied by NADPH–cytochrome P-450 reductase, a flavoprotein that transfers electrons from NADPH (the reduced form of nicotinamide-adenine dinucleotide phosphate) to cytochrome P-450. Cytochrome P-450 enzymes are grouped into 14 mammalian gene families that share sequence identity and 17 subfamilies. They are designated by a root symbol CYP, followed by an Arabic number for family, a letter for subfamily, and another Arabic number for the specific gene. Enzymes in the 1A, 2B, 2C, 2D, and 3A subfamilies are most important in mammalian metabolism; CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are important in human metabolism. The specificity of the enzymes helps explain many drug interactions. Examples of drugs that interact with specific cytochrome P-450 enzymes are listed in TABLE 298–3 (see also DRUG INTERACTIONS in Ch. 301). Genetic differences among patients may alter response.

Conjugation: Glucuronidation, the most common phase II reaction, is the only one that occurs in the liver microsomal enzyme system. Glucuronides are secreted in bile and eliminated in urine. Chloramphenicol, meprobamate, and morphine are metabolized this way. Amino acid conjugation with glutamine or glycine produces conjugates (eg, salicyluric acid formed from salicylic acid and glycine) that are readily excreted in urine but are not extensively secreted in bile. Acetylation is the primary metabolic pathway for sulfonamides. Hydralazine, isoniazid, and procainamide are also acetylated. Sulfoconjugation is the reaction between phenolic or alcoholic groups and inorganic sulfate, which is partially derived from sulfur-containing amino acids (eg, cysteine). The sulfate esters formed are polar and readily excreted in urine. Drugs that form sulfate conjugates include acetaminophen, estradiol, methyldopa, minoxidil, and thyroxine. Methylation is a major metabolic pathway for inactivation of some catecholamines. Niacinamide and thiouracil are also methylated.

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TABLE 298–3. SOME SUBSTANCES THAT INTERACT WITH CYTOCHROME P-450 ENZYMES

Enzyme	Substrates	Inhibitors	Inducers
CYP1A2	Acetaminophen Estradiol Theophylline Verapamil Warfarin	Furafylline	Charcoal-broiled beef Cigarette smoke
CYP2C9	Diclofenac Phenytoin Piroxicam Tetrahydrocannabinol Tolbutamide	Sulfaphenazole Sulfinpyrazone	Rifampin
CYP2C19	Diazepam Hexobarbital Omeprazole Pentamidine Propranolol	Tranylcypromine	Rifampin
CYP2D6	Debrisoquin Desipramine Encainide Mexiletine Nortriptyline	Fluoxetine Quinidine	None known
CYP3A4	Amiodarone Lovastatin Nifedipine Tamoxifen Terfenadine	Ketoconazole Troleandomycin	Carbamazepine Phenobarbital

Age-Related Changes

Because newborns have partially developed liver microsomal enzyme systems, they have difficulty metabolizing many drugs (eg, hexobarbital, phenacetin, amphetamine, chlorpromazine). In newborns, slower conversion to glucuronide can have serious effects. For example, equivalent mg/kg doses of chloramphenicol that are well tolerated by older patients can result in the gray baby syndrome and in prolonged elevated blood levels of chloramphenicol.

Elderly patients often have a reduced ability to metabolize drugs. The reduction varies depending on the drug and is not as severe as that in newborns (see Ch. 304).

Individual Variation

Because of individual variation (see also VARIABILITY IN PARAMETER VALUES in Ch. 299), predicting the clinical response to a given dose of a drug is difficult. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not achieved; in others, metabolism may be so slow that usual doses produce toxic effects. For example, plasma phenytoin concentrations at steady state vary from 2.5 to > 40 mg/L (10 to > 160 µmol/L) in different patients given a daily dose of 300 mg. Some variation is due to differences in the amount of the key enzyme, CYP2C9, available in the liver and to differences in the affinity of the enzyme for the drug. Genetic factors play a major role in determining these differences. Concurrent diseases (particularly chronic liver disease) and drug interactions (especially those involving induction or inhibition of metabolism) also contribute.

Capacity Limitation

For almost any drug, the rate of metabolism of any enzyme in any given pathway reaches an upper limit (capacity limitation). At therapeutic concentrations, usually only a small fraction of the enzyme sites are occupied, and the rate of metabolism increases with drug concentration. Occasionally, when most of the enzyme sites are occupied, the rate of metabolism does not increase in proportion to drug concentration. The result is capacity-limited metabolism. Phenytoin and alcohol have this type of metabolism, which helps explain the interpatient variability in phenytoin concentrations after a fixed daily dose of 300 mg.

EXCRETION

Process by which a drug or a metabolite is eliminated from the body without further chemical change.

The kidneys, which excrete water-soluble substances, are the major organs of excretion. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Although excretion via breast milk may not be important to the mother, it may be to the suckling infant (see DRUGS IN LACTATING MOTHERS in Ch. 256).

Renal Excretion

Glomerular filtration and tubular reabsorption: About 1/5 of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; the remainder passes through the efferent arterioles surrounding the renal tubules. Drugs bound to plasma proteins are not filtered; only unbound drug is contained in the filtrate. The principles of transmembrane passage govern renal tubular reabsorption of drugs. Polar compounds and ions cannot diffuse back into the circulation and are excreted unless a specific transport mechanism for their reabsorption exists (eg, as for glucose, ascorbic acid, and B vitamins).

Effects of urine pH: The glomerular filtrate that enters the proximal tubule has the same pH as plasma, but the pH of voided urine varies from 4.5 to 8.0. This variation in pH may markedly affect the rate of drug excretion. Because un-ionized forms of nonpolar weak acids and weak bases tend to be reabsorbed readily from tubular fluids, acidification of urine increases reabsorption (ie, decreases excretion) of weak acids and decreases reabsorption (ie, increases excretion) of weak bases. The opposite occurs after alkalinization of urine.

In some cases of overdose, these principles may be applied to enhance the excretion of weak acids or bases. For example, alkalinization of urine increases the excretion of the weak acids phenobarbital and aspirin, and acidification may accelerate the excretion of bases, such as methamphetamine. The extent to which changes in urinary pH alter the rate of drug elimination depends on the contribution of the renal route to total elimination as well as on the polarity of the un-ionized form and the degree of ionization of the molecule.

Tubular secretion: Mechanisms for active tubular secretion in the proximal tubule are important in the elimination of many drugs (eg, penicillin, mecamylamine, salicylic acid). This energy-dependent process may be blocked by metabolic inhibitors. When drug concentration is high, an upper limit for secretory transport can be reached; each substance has a characteristic maximum secretion rate (transport maximum).

Anions and cations are handled by separate transport mechanisms. Normally, the anion secretory system eliminates metabolites conjugated with glycine, sulfate, or glucuronic acid. Anionic compounds compete with one another for secretion. This competition can be used therapeutically; eg, probenecid blocks the normally rapid tubular secretion of penicillin, resulting in higher plasma penicillin concentrations for a longer time. Organic cations compete with each other but usually not with anions.

Age-related changes: With aging, renal drug excretion decreases (see PHARMACOKINETICS in Ch. 304 and TABLE 304–1).

Biliary Excretion

Drugs and their metabolites that are extensively excreted in bile are transported across the biliary epithelium against a concentration gradient, requiring active secretory transport. Secretory transport may approach an upper limit at high plasma concentrations of a drug (transport maximum), and substances with similar physicochemical properties may compete for excretion via the same mechanism.

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Drugs with a mol wt > 300 g/mol (smaller molecules are generally excreted only in negligible amounts) and with both polar and lipophilic groups are more likely to be excreted in bile. Conjugation, particularly with glucuronic acid, also leads to biliary excretion.

In the **enterohepatic cycle**, a drug secreted in bile is reabsorbed from the intestine. Drug conjugates secreted into the intestine also undergo enterohepatic cycling when they are hydrolyzed and the drug is reabsorbed. Biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete, when some of the secreted drug is not reabsorbed from the intestine.

299 / PHARMACOKINETICS

Study of the time course of a drug and its metabolites in the body after administration by any route.

An appropriate response to a drug requires the appropriate concentration of drug at the site of action. The dosage regimen required to attain and maintain the appropriate concentration depends on pharmacokinetics. The appropriate concentration and dosage regimen depend on the patient's clinical state, severity of the disorder, presence of concurrent disease, use of other drugs, and other factors.

Because of individual differences, drug administration must be based on each patient's needs—traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because optimal response may be delayed or serious toxic reactions may occur. Alternatively, a drug can be administered according to its expected absorption and disposition (distribution and elimination—see also Ch. 298) in a patient, and dosage can be adjusted by monitoring plasma drug concentration and drug effects. This approach requires knowledge of the drug's pharmacokinetics as a function of the patient's age and weight, and the kinetic consequences of concurrent diseases (eg, renal, hepatic, or cardiovascular disease or a combination of diseases).

BASIC PHARMACOKINETIC PARAMETERS

The pharmacokinetic behavior of most drugs can be summarized by the following parameters, whose formulas are listed in TABLE 299-1. The parameters are constants, although their values may differ from patient to patient and in the same patient under different conditions.

Bioavailability expresses the extent of drug absorption into the systemic circulation (see Ch. 298). The **absorption rate constant** expresses the speed of absorption. These parameters influence the maximum (peak) concentration, the time at which the maximum concentration occurs (peak time), and the area under the concentration-time curve (AUC) after a single oral dose. During long-term drug therapy, the extent of absorption is the more important measurement because average concentration depends on it; the degree of fluctuation is related to the absorption rate constant.

The apparent volume of distribution is the amount of fluid that would be required to contain the drug in the body at the same concentration as in the blood or plasma. It can be used to estimate the dose required to produce a given concentration and the concentration expected for a given dose. The unbound concentration is closely associated with drug effects, so **unbound fraction** is a useful measure, particularly when plasma protein binding is altered—eg, by hypoalbuminemia, renal or hepatic disease, or displacement interactions. The apparent volume of distribution and the unbound fraction in plasma are the most widely used parameters for drug distribution (see Ch. 298).

The rate of elimination of a drug from the body varies with the plasma concentration. The parameter relating elimination rate to plasma concentration is **total clearance**, which equals renal clearance plus extrarenal (metabolic) clearance (see also Estimation of Parameter Values in Ch. 303).

TABLE 299–1. FORMULAS DEFINING BASIC PHARMACOKINETIC PARAMETERS

Category	Parameter	Formula
Absorption	Absorption rate constant	= Rate of drug absorption ÷ Amount of drug remaining to be absorbed
	Bioavailability	= Amount of drug absorbed ÷ Drug dose
Distribution	Apparent volume of distribution	= Amount of drug in body ÷ Plasma drug concentration
	Unbound fraction	= Plasma concentration of unbound drug ÷ Plasma drug concentration
Elimination	Rate of elimination	= Renal excretion + Extrarenal (usually metabolic) elimination
	Clearance	= Rate of drug elimination ÷ Plasma drug concentration
	Renal clearance	= Rate of renal excretion of drug ÷ Plasma drug concentration
	Metabolic clearance	= Rate of drug metabolism ÷ Plasma drug concentration
	Fraction excreted unchanged	= Rate of renal excretion of drug ÷ Rate of drug elimination
	Elimination rate constant	= Rate of drug elimination ÷ Amount of drug in body
		= Clearance ÷ Volume of distribution
	Biologic half-life	= 0.693 ÷ Elimination rate constant

The **fraction excreted unchanged** helps assess the potential effect of renal and hepatic diseases on drug elimination. A low fraction indicates that hepatic metabolism is the likely mechanism of elimination and that hepatic disease may therefore affect drug elimination. Renal diseases produce greater effects on the kinetics of drugs with a high fraction excreted unchanged.

The extraction rate of a drug from the blood by an eliminating organ, such as the liver, cannot exceed the rate of drug delivery to the organ. Thus, clearance has an upper limit, based on drug delivery and hence on blood flow to the organ. Furthermore, when the eliminating organ is the liver or gut wall and a drug is given orally, part of the dose may be metabolized as it passes through the tissues to the systemic circulation; this process is called **first-pass metabolism**. Thus, if extraction (clearance) of a drug is high in the liver or gut wall, oral bioavailability is low, sometimes precluding oral administration or requiring an oral dose much larger than an equivalent parenteral dose. Drugs with extensive first-pass metabolism include alprenolol, hydralazine, isoproterenol, lidocaine, meperidine, morphine, nifedipine, nitroglycerin, propranolol, testosterone, and verapamil.

The **elimination rate constant** is a function of how a drug is cleared from the blood by the eliminating organs and how the drug distributes throughout the body.

Half-life (elimination) is the time required for the plasma drug concentration or the amount of drug in the body to decrease by 50%. For most drugs, half-life remains the same regardless of how much drug is in the body. Exceptions include phenytoin, theophylline, and heparin.

Mean residence time (MRT), another measure of drug elimination, is the average time a drug molecule remains in the body after rapid IV injection. Like clearance, its value is independent of dose. After an IV bolus,

$$MRT = \frac{AUMC}{AUC}$$

AUMC is the area under the first moment of the plasma concentration-time curve. For a drug with one-compartment distribution characteristics, MRT equals the reciprocal of the elimination rate constant.

DRUG ADMINISTRATION

The kinetic consequences of administering a drug in a single dose (IV or oral), by constant-rate infusion, and in multiple oral doses are described below, using theophylline (given as aminophylline) as an example. The metabolism of theophylline is concentration-dependent in some persons, especially children. In this example, the drug is given to a 70-kg patient (patient A) who has concentration-independent metabolism and the following parameters: bioavailability, 1.0; absorption rate constant, 1.0/h; apparent volume of distribution, 0.5 L/kg; clearance, 43 mL/h/kg; and half-life, 8 h.

Single Dose

Intravascular: After a single 320-mg IV dose of aminophylline (hydrous form is 80% theophylline) is given to patient A (see Fig. 299–1), the predicted initial plasma concentration of theophylline is 7.3 mg/L (41 μmol/L)—ie, dose (256 mg) divided by apparent volume of distribution (0.5 L/kg × 70 kg = 35 L). The subsequent decline is estimated from the half-life; every 8 h, the concentration decreases by a factor of 2.

The discrepancy between the observed (solid line) and predicted (broken line) concentration-time profiles in the first 2 h is explained by the time required to distribute the drug throughout the body (distribution phase). Because drug distribution requires time, single IV doses of many drugs, including aminophylline, must be given by short-term infusion over ≥ 5 to 10 min to avoid side effects.

Extravascular: After a single 300-mg oral dose of aminophylline (anhydrous form, often used orally, is 85% theophylline) is given to patient A (see Fig. 299–2), the time course differs from that of a single IV dose (see Fig. 299–1) because time is required to absorb the drug. However, AUC is the same because this drug is virtually completely absorbed. The more rapid the absorption, the closer the curve is to that of the IV dose. The time of peak concentration is when the absorption rate equals the elimination rate; absorption is not complete at this time.

Constant-Rate Infusion

Plateau concentration: In patient A, after an IV infusion of aminophylline at a constant rate of 45 mg/h (see curve A in Fig. 299–3), the plasma concentration and amount of theophylline in the body increase until the elimination rate equals the infusion rate. The plasma concentration and the amount of drug in the body are then at steady state—a plateau. Based on the formulas for clearance and elimination rate constant (see Table 299–1), infusion rate equals clearance times plateau plasma drug concentration or equals elimination rate constant times plateau amount of drug in the body. Thus, the plateau plasma concentration is determined only by clearance and infusion rate, and the plateau amount of drug in the body is determined only by the elimination rate constant and infusion rate.

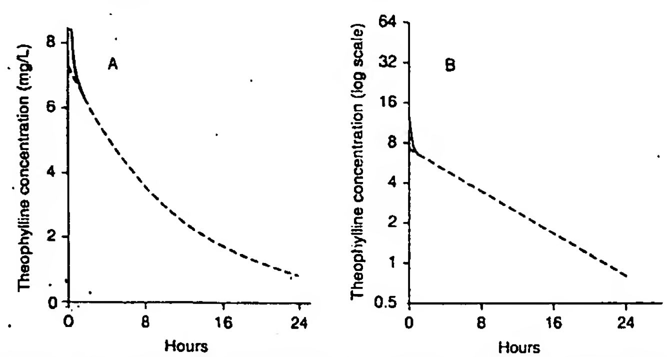

FIG. 299–1. Decline of plasma theophylline concentration in patient A after IV administration of a single 320-mg dose of aminophylline. Shown on linear (A) and semilogarithmic (B) plots. Observed curve = (——); predicted curve from given parameter values = (– – –).

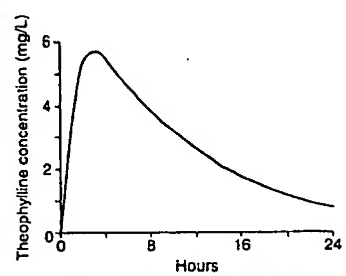

FIG. 299–2. Time course of plasma theophylline concentration after oral administration of a single 300-mg dose of aminophylline to patient A.

Time to reach plateau: The time required for theophylline to accumulate in the body (and then to disappear) depends on the drug's half-life, as shown in Fig. 299–3. A single IV 530-mg bolus of aminophylline produces a theophylline concentration of 12 mg/L (67 μmol/L); the bolus is followed immediately by an infusion of 45 mg/h to maintain the initial concentration (curve B in Fig. 299–3). Drug from the loading dose disappears (curve C), with 1/2 remaining at one half-life, 1/4 at two half-lives, and so on. Without the loading dose, the amount of drug in the body from the infusion (curve A) increases so that 1/2 of the plateau amount is present at one half-life, 3/4 at two half-lives, and so on.

If the infusion is stopped at 48 h, the post-infusion curve resembles curve C. Without a loading dose, aminophylline must be infused for at least 32 h (four half-lives) for the concentration to approach plateau in patient A. A plasma concentration measurement made after the plateau estimates theophylline clearance.

The principles for IV infusion apply to any constant-rate input (eg, to constant-rate devices used in transdermal, intraocular, oral, and intrauterine drug delivery). Plateau plasma concentration and the time to reach

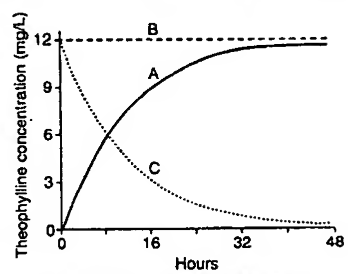

FIG. 299–3. Time course of plasma theophylline concentration after a 45-mg/h constant-rate IV infusion of aminophylline without and with a 530-mg IV loading dose in patient A. A = without loading dose; B = with loading dose; C = drug remaining from loading dose.

it depend on clearance and half-life, respectively, as for IV infusions. Bioavailability is an additional factor applicable to extravascular administration.

Multiple Oral Doses

Drug accumulation: Repetitive administration of aminophylline 300 mg po q 6 h to patient A increases the theophylline concentration (see curve A in Fig. 299–4). As with

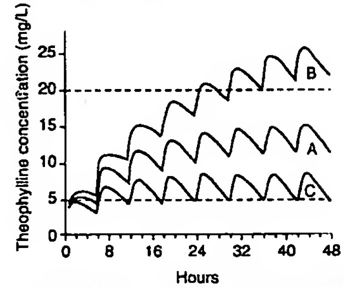

FIG. 299–4. Accumulation of theophylline after oral administration of aminophylline 300 mg q 6 h. Curve A = patient A; curve B = patient B, whose clearance is 1/2 that of patient A; curve C = patient C, whose clearance is twice that of patient A. The dashed lines are the usual therapeutic limits, representing the therapeutic window.

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IV infusion, the average plateau concentration depends on clearance, and the time required for the drug to accumulate depends on half-life. Here, however, plasma concentrations fluctuate because dosing is intermittent.

If theophylline clearance is altered, eg, by disease, pharmacokinetics change (curves B and C). Patient B has heart failure with a clearance of 21.5 mL/h/kg (about half that of patient A). After patient B is given aminophylline 300 mg q 6 h, drug concentration is double that of patient A (curve B), and the time to reach plateau levels is twice as long because half-life (16 h) is twice that in a healthy adult. Plasma theophylline concentrations of 10 to 20 mg/L (55 to 110 μmol/L) are usually optimal. Above 20 mg/L, toxicity is more likely. Thus, patient B is at risk of toxicity (nausea, vomiting, CNS stimulation, seizures), which, with the knowledge that heart failure decreases metabolism, may be averted by giving a smaller dose. Also, slow metabolism may be detected by monitoring plasma concentration.

Dosage regimens: For patient B, aminophylline 200 mg q 8 h (25 mg/h) is probably appropriate. However, because of the long half-life and the slow accumulation in this patient, a loading dose must be given to rapidly produce a therapeutic concentration (and response). The required loading dose of aminophylline is the apparent volume of distribution times the desired theophylline concentration, corrected by the fraction of theophylline in aminophylline, or about 500 mg:

$$35\ L \times \frac{12\ mg}{L} \times \frac{100\ mg\ aminophylline}{85\ mg\ theophylline}$$

In a young, otherwise healthy asthmatic adult who is a heavy smoker (patient C), theophylline clearance is 86 mL/h/kg, and half-life is 4 h. Aminophylline 300 mg q 6 h (50 mg/h) is probably ineffective (see curve C in Fig. 299-4). The need for more drug can be anticipated and may be confirmed by measuring plasma concentration just before the next dose. However, giving aminophylline to this patient is difficult because of the short half-life, high clearance, and large dosage requirements (100 mg/h). For this patient, a prolonged-release formulation is indicated. Because absorption is more or less sustained, 600 mg q 6 h will probably prevent concentrations from fluctuating widely.

VARIABILITY IN PARAMETER VALUES

Many factors affecting pharmacokinetic parameters should be considered when tailoring drug administration for a particular patient. Even with dosage adjustment, however, sufficient variability usually remains; thus, drug response and, in some cases, plasma drug concentration must be closely monitored.

Age and weight: For some drugs, the effects of age and weight on pharmacokinetics are well established. For persons aged 6 mo to 20 yr, renal function appears to correlate well with BSA. Thus, for drugs primarily eliminated unchanged by renal excretion, clearance in children varies with age according to change in BSA. For persons > 20 yr, renal function decreases about 1%/yr. Thus, dosage of these drugs can be adjusted by age. BSA also correlates with metabolic clearance in children, although exceptions are common. For newborns and infants, renal and hepatic functions are not fully developed, and generalizations, except for the occurrence of rapid change, are less accurate.

Renal function impairment: Renal clearance of most drugs appears to vary directly with creatinine clearance, regardless of which renal disease is present. The change in total clearance depends on the contribution of the kidneys to total elimination. Thus, total clearance should be proportional to renal function (creatinine clearance) for drugs excreted unchanged and to be unaffected for drugs eliminated by metabolism.

Renal failure may change the apparent volume of distribution, which decreases for digoxin because of decreased tissue binding and increases for phenytoin, salicylic acid, and many other drugs because of decreased binding to plasma proteins.

Physiologic stress: Concentration of the acute-phase protein α_1-acid glycoprotein increases during physiologic stress (eg, MI, surgery, ulcerative colitis, Crohn's disease). Consequently, the binding of several drugs (eg, propranolol, quinidine, disopyramide) to this protein increases, and the apparent volume of distribution of these drugs decreases accordingly.

Hepatic disease: Hepatic dysfunction can change metabolic clearance, but good correlates or predictors of the changes are unavailable. Hepatic cirrhosis can dramatically reduce drug metabolism and often results in reduced plasma protein binding because of lowered plasma albumin. Acute hepatitis, with elevated serum enzymes, usually does not alter drug metabolism.

Other diseases: Heart failure, pneumonia, hyperthyroidism, and many other diseases can alter the pharmacokinetics of drugs.

Drug interactions: Pharmacokinetic parameter values and, therefore, drug response may be affected by drug interactions. Most interactions are graded, and the extent of the interaction depends on the concentrations of both drugs. Thus, determining and adjusting drug dosage is difficult (see Drug Interactions in Ch. 301).

Dosage: In some instances, changes in dose, dosing rate, or duration of therapy alter a drug's kinetics. For example, as dose is increased, the bioavailability of griseofulvin decreases because of the drug's low solubility in the fluids of the upper GI tract. For phenytoin, steady-state plasma concentration increases disproportionately when dosing rate is increased, because the metabolizing enzyme has a limited capacity to eliminate the drug, and the usual dosing rate approaches the maximum rate of metabolism. Plasma carbamazepine concentration decreases during long-term use because carbamazepine induces its own metabolism. Other causes of dosage-dependent kinetic changes are saturable plasma protein and tissue binding (eg, phenylbutazone), saturable secretion in the kidneys (eg, high-dose penicillin), and saturable metabolism during the first pass through the liver (eg, propranolol).

300 / PHARMACODYNAMICS

Study of the biochemical and physiologic effects of drugs and their mechanisms of action.

Many drugs produce pharmacologic responses by interacting with (binding to) specific macromolecules, usually complex proteins, on or within cells. Some drug classes react directly with endogenous or exogenous nonprotein substances; included are some cancer chemotherapeutic drugs that interact with nucleic acids, metal chelating drugs (eg, calcium disodium edetate, dimercaprol, deferoxamine), and antacids used to chemically neutralize gastric acid.

DRUG-RECEPTOR INTERACTIONS

Few if any drugs have absolute specificity, but most have relative selectivity; eg, atropine inhibits the actions of acetylcholine on exocrine glands and smooth muscles, but not on skeletal muscle. The action of such selective drugs results from their physicochemical binding to cellular components called receptors. Physiologic receptors are macromolecules involved in chemical signaling between and within cells. A molecule that binds to a receptor is called a ligand. When a ligand (hormone, neurotransmitter, intracellular messenger molecule, or exogenous drug) combines with a receptor, cell function changes (see Table 300–1). Each ligand may interact with multiple receptor subtypes. Activated receptors directly or indirectly regulate cellular biochemical processes (eg, ion conductance, protein phosphorylation, DNA transcription). In many cases, receptors within the cell membrane are coupled through guanine nucleotide-binding proteins (G proteins) to various effector systems involving intracellular second messenger molecules.

Receptors are dynamic, influenced by external factors as well as by intracellular regulatory mechanisms. Receptor up-regulation and down-regulation are relevant to clinically important adaptation to drugs (desensitization, tachyphylaxis, tolerance, acquired resistance, postwithdrawal supersensitivity).

Recognition sites are the precise molecular regions of receptor macromolecules to which ligands bind. A drug may interact at the same site as an endogenous agonist (hormone or neurotransmitter) or at a different site. Agonists that bind to an adjacent or a different site are sometimes termed allo-

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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1991-1994- Research Fellow, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1994-1996 Research Associate, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1996-2001 Scientist, Therapeutic Drug Delivery, BD Technologies, RTP, NC
2001-present Sr. Scientist, Manager, Therapeutic Drug Delivery, BD Technologies, RTP, NC

Honors and Professional Memberships

1990-present Member, American Association of Pharmaceutical Sciences
2003-present Member, Controlled Release Society
2000-present Member, BD Technologies Institutional Animal Care and Use Committee
2001 Wesley J. Howe Award for Technology Innovation, corporate achievement award

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2. United States Patent 6,595,947 July 22, 2003, Topical delivery of vaccines; JA Mikszta; JM Brittingham; J Alarcon; **RJ Pettis**; JP Dekker III
3. United States Patent 6,607,513 August 19, 2003, Device for withdrawing or administering a substance and method of manufacturing a device; J. Down; NG Harvey; FE Martin; **RJ Pettis**, AG Lastovich
4. United States Patent 6,656,147 December 2, 2003 Method and delivery device for the transdermal administration of a substance; M Gertsek; BM Wilkinson; **RJ Pettis**
5. United States Patent 6,689,100 February 10, 2004 Microdevice and method of delivering or withdrawing a substance through the skin of an animal; RI Connelly, **RJ Pettis**
6. United States Patent 6,722,364 April 20, 2004 Medicament inhalation delivery devices and methods for using the same; RI Robert; VJ Sullivan; CD Shermer; A Bhuta; **RJ Pettis**
7. United States Patent 6,808,506. October 26, 2004, Device and method for delivering or withdrawing a substance through the skin, AG Lastovich; JK Fentress; J Griggs; **RJ Pettis**; D Sutter; FE Martin; MI Haider
8. United States Patent 6,858,018 February 22, 2005, Iontophoretic devices, PG Green; **RJ Pettis**; MR Brosnan-Cook
9. United States Patent 7,040,316 May 9, 2006, Medicament inhalation delivery devices and methods for using the same; RI Connelly; VJ Sullivan; CD Shermer; A Bhuta; **RJ Pettis**
10. United States Patent 7,060,059 June 13, 2006, System and method for initiating and maintaining continuous, long-term control of a concentration of a substance in a patient using a feedback or model-

based controller coupled to a single-needle or multi-needle intradermal (ID) delivery device, S Keith; RS Parker; NG Harvey; **RJ Pettis**, JD DeNuzzio; G Vonk

11. United States Patent United States Patent 7,083,592, August 1, 2006, Device and method for delivering or withdrawing a substance through skin, AG Lastovich, JK Fentress, J Griggs, **RJ Pettis**, D Sutter, FE Martin, MI Haider,
12. 37 patents pending

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